REMARKS

Status of the Claims

Claims 93-102, 126-137,139-156, and 173 are currently pending in the present application. Claims 1-92, 103-125, 138, and 157-172 have been canceled without prejudice or disclaimer of the subject matter claimed therein. Claims 93-102, 126-137, and 139-156 have been amended. New claim 173, dependent from claim 156 and directed to the elected invention, has been added.

Withdrawn Claims

Since Applicants elected Group VII, directed to claims 93-102, 126-137, and 139-156, as the claimed invention, these claims and new claim 173 are currently under examination. Accordingly, the statement on page 3 of the Office Action, dated March 16, 2006, indicating that claim 156 has been withdrawn from further consideration is an inadvertent error.

Amendments to the Specification

Under the Brief Description of Drawings, the descriptions for figures 7, 8, 10, 12, 15-18, and 21 have been amended to insert references to the subfigures.

In the Brief Description of the Drawings, the description of figure 10 has been amended to include a description for the open and filled symbols. Support for the amendment can be found on page 49, line 31 to page 50, line 5.

In the Brief Description of the Drawings, the description of figure 17 has been amended to correct a typographical error. The Greek symbol "β" has been inserted in line 4 before "-gal." Support for the amendment can be found on page 54, line 26.

The amendments to the specification do not introduce prohibited new matter.

Amendments to the Claims

Claims 92, 139, and 156 have been amended to provide separate embodiment of the invention. Support for the amendments can be found on page 18, line 3 and on page 22, line 14 and in the claims as originally filed.

Claims 94-102, 126-137, and 140-155 have been amended to replace the article "A" with "The."

Claims 93, 98, 139, 141, 144, and 151-154 have also been amended to insert "thereof" after "fragment" for consistency in claim language. Support for this amendment can be found in claim 97 and on page 8, line 6.

New claim 173 has been added. Support for the new claim can be found in claim 155.

The amendments to the claims do not introduce prohibited new matter.

Related Applications

The attached communication provides a list of technically related applications for the Examiner's consideration.

Applicants respectfully point out that similar rejections were made in related U.S. patent application 10/308,183, but have now been withdrawn and that U.S. patent application 10/308,183 has issued as U.S. Patent 7,090,985.

Objections to Claims

Claims 95 and 155 are objected to as encompassing non-elected subject matter.

Applicants respectfully point out that the Office Action (Restriction/Election Requirement), dated December 29, 2005, indicated that the Invention of Group VII, which includes claims 95 and 155, encompasses patentably distinct species. In response to the Office Action, dated December 29, 2005, Applicants elected N-alkylated 2-oxo-pyrrolidine derivatives. However, the Office Action, dated March 16, 2006, has not identified any prior art disclosing the elected species.

Moreover, Applicants point out that when a generic claim is found to be allowable, the restriction requirement as to the encompassed species must be withdrawn and the corresponding claims directed to the encompassed species should no longer be withdrawn from consideration. MPEP 809.03.

Oath/Declaration

The declaration has been objected to as being defective for failing to recite the serial number of the application.

Applicants respectfully point out that the application number need not be completed in the declaration in order to adequately identify the application (see MPEP § 602(VI)). A

combination of information such as the names of the inventors, the attorney docket number, and/or the title of the application is adequate to identify the application (see also 37 CFR 1.63).

Drawings

Figure 10 has been objected to because it does not include a legend describing the open and filled symbols. The Brief Description of the Drawings for figure 10 has been amended to include a description for the open and filled symbols.

Figures 12A and 12 B have been objected to for failing to provide labels for the lanes. Applicants respectfully point out that the lanes in figures 12A and 12B were labeled as filed. Attached is a replacement copy of figures 12A and 12B.

Figures 17A and 17B have been objected to because they do not include a legend describing the open/filled histograms and symbols. Applicants respectfully point out that the Brief Description of the Drawings for figures 17A and 17B provides a description for the open/filled histograms and symbols (see page 17, lines 9-15 of the specification).

Rejections of the Claims Under 35 U.S.C. § 112, First Paragraph

A. Claims 93-102, 126-137, and 139-156 have been rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable the scope of the invention as claimed. The Office Action alleges that the specification, while being enabling for identifying the binding of levetiracetam (LEV), LEV analog ucb30889, ucb101282-1 to the LEV binding Site (LBS) of SV2A, does not provide enablement for all LEV analogs and derivatives binding to the LBS of SV2A protein, or all compounds that modulate the different activities of SV2 proteins and are useful for treating all neurological disorders associated with synaptic function as broadly claimed.

Applicants respectfully point out that the claims as they stand are directed to a method of identifying compounds or agents that bind an SV2 protein and modulate an activity of an SV2 protein or are useful in the treatment of a neurological or endocrinological disease. The inventors of the present invention have shown that SV2 proteins contain a LBS. Thus, the present invention is based in part on the unexpected finding that LEV and its analogs and derivatives interact with the SV2 protein. Based on this finding, the inventors developed the claimed method of identifying new compounds and agents that bind an SV2 protein and

modulate an activity of an SV2 protein or are useful in the treatment of a neurological or endocrinological disorder.

The claims as they stand are directed to methods of identifying new compounds or agents that interact with the SV2 protein comprising using an SV2 protein or fragment thereof containing a LBS. Also, the claims are directed to methods of identifying new agents or compounds that compete with LEV or its analogs and derivatives for interacting with an SV2 protein and that are useful in the treatment of a neurological or endocrinological disease. Agents or compounds that bind or compete with LEV and its analogs or derivatives for binding an SV2 protein include agents or compounds that inhibit the binding of LEV and its analogs or derivatives to an SV2 protein.

In one embodiment, if the agent or compound binds an SV2 protein, then it would also modulate an activity of an SV2 protein and compete with LEV or an analog or derivative thereof for binding an SV2 protein. The present invention can detect both direct competition with LEV or its analog or derivatives thereof for binding to an SV2 protein as well as modulation of an activity of an SV2 protein and the usefulness of a compound or agent in the treatment of a neurological or endocrinological disease.

However, if the agent or compound does not bind an SV2 protein, then it would not compete with LEV or an analog or derivative thereof. Moreover, such an agent or compound would not inhibit the binding of LEV to an SV2 protein and would not be useful in treating a neurological or endocrinological disease.

The specification teaches that LEV and various LEV analogs and derivatives interact with SV2 proteins. As an example, the specification discloses assays showing that LEV interacts with the SV2A protein and such interaction can be used to identify agents or compounds that bind and modulate an activity of an SV2A protein or that compete with and inhibit the binding of LEV or its analog or derivative thereof to an SV2A protein. Applicants respectfully submit that the specification enables the methods of the claimed invention. The burden is on the Patent Office to provide evidence that the claimed invention is not enabled by the specification. *In re Marzocchi*, 169 USPQ 367 (1971). In this case, the Patent Office has not provided sufficient reason to doubt that the claimed method can be used to identify compounds that bind and modulate an activity of an SV2 protein or that compete with LEV or its analog or derivative for binding to the LBS and are useful in the treatment of neurological diseases.

Moreover, Applicants respectfully point out that the SV2 proteins are a well known family of snyaptic vesicle proteins (see attached Janz *et al.* Neuroscience, 1999, 94(4): 1279-1290). SV2 proteins are structurally and functionally related proteins. Three SV2 proteins, SV2A, SV2B, and SV2C, have been cloned and characterized. As shown by Janz *et al.*, these proteins are highly homologous glycoproteins found on synaptic vesicles. They contain 12 highly conserved transmembrane regions and three glycosylation sites. They are recognized by the same monoclonal SV2 antibody. Based on their structural similarity, one would reasonably expect them to function in a similar manner. Accordingly, the assays provided by the specification for the SV2A proteins are applicable to the other SV2 proteins.

Further, Applicants respectfully submit that that the claimed invention is based on the finding that the activity of LEV, a widely used antiepileptic drug, is mediated by the SV2A protein. Lynch *et al.* (PNAS, 2004, 101(26): 9861-9866, submitted with IDS of September 23, 2004) disclose that the SV2A protein contains a binding site for LEV. Lynch *et al.* show that LEV and related compounds bind to the SV2A protein expressed in fibroblasts suggesting that the protein is sufficient for LEV binding. Brain membranes and purified synaptic vesicles from mice lacking the SV2A protein do not bind a tritiated LEV derivative, indicating that the SV2A protein is necessary for LEV binding. Figure 5 of Lynch *et al.* also shows that there is a high degree of correlation between binding affinities of a series of LEV derivatives to the SV2A protein recombinantly expressed in fibroblasts and to LEV-binding in brain.

Since LEV is a well-known antiepileptic drug, agents or compounds that compete with LEV for interacting with the SV2 protein or modulate the interaction of LEV and the SV2 protein would also likely be effective antiepileptics because such agents, or compounds interact with the SV2 protein in a manner like or identical to LEV. As shown by Lynch *et al.*, there is a strong correlation between the affinity of a compound for SV2A and its ability to protect against seizures in an audiogenic mouse animal model of epilepsy. Specifically, Figure 6 in Lynch *et al.* discloses a correlation between binding affinities for SV2A and anti-seizure potency of LEV derivatives in the audiogenic mouse model of epilepsy. As discussed on page 9865 (left column), these data are consistent with the previous report of a correlation between binding of LEV analogs in rat brain and antiseizure potency. Lynch *et al.* also confirmed that at concentrations of up to 100 μM, none of the non-LEV related anti-epileptic drugs (AEDs) such as valproate, carbamazepine, phenytoin, ethosuximide, felbamate, gabapentin, tiagabine, and

zonisamide, competed with [^{3}H]ucb 30889 for binding SV2A. ([^{3}H]ucb 30889 is a photoactivable derivative of LEV and behaves as a surrogate for LEV.) This is consistent with results from previous screening of a large number of AEDs failing to identify any AEDs with high affinity for the LEV-binding site.

Further, the use of LEV and its analogs or derivatives to treat various neurological and endocrinological diseases are known. U.S. Patent 6,903,130 (see attached) discloses the use of LEV for the treatment of bipolar disorders, mania, migraine, and chronic or neuropathic pain, and WO 02/067931 (see attached) discloses the use of pyrrolidones including LEV for the treatment of various hyperkinetic disorders such as Tourette syndrome, tics, and tremors.

Given the teachings of the present specification and the information provided by the prior art regarding LEV and SV2 proteins, it is within the skill of the artisan to identify compounds or agents that bind to and modulate an activity of an SV2 protein or that compete with LEV or its analogs or derivatives for binding an SV2 protein and are useful in treating neurological and endocrinological diseases. Since LEV and SV2 proteins are well known molecules, it would not require undue experimentation to practice the claimed invention. Accordingly, the specification enables the claimed methods of using cell-free or membrane-free SV2 protein or fragment thereof for identifying new agents or compounds that interact with an SV2 protein or are useful in treating neurological or endocrinological diseases.

B. Claims 93-102, 126-137, and 139-156 have been rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement for the genus of LEV analogs or derivatives.

The Office Action alleges that written description is lacking for the broad genus of analogs or derivatives of LEV. Applicants respectfully point out that the claims as they stand are directed to methods of identifying compounds or agents that interact with the SV2 protein. The claims use an SV2 protein comprising an LBS in identifying new compounds or agents that interact with SV2 proteins. The compounds or agents identified by the claimed method may be a LEV analog or derivative. However, the claims are not directed to analogs or derivatives of LEV.

Applicants respectfully submit that the specification on pages 12-15 describes analogs and derivatives of LEV in detail. The specification provides specific examples of analogs and

derivatives of LEV and discloses alternative substituents on LEV for obtaining analogs and derivatives. Specifically, on page 14, the specification defines "LEV analogs or derivatives thereof" as including any acetam compound of formula I comprising R groups, wherein the R groups have defined structures. Accordingly, there is sufficient description for the use of "analogs and derivatives of LEV" in the presently claimed methods of identifying compounds and agents that interact with an SV2 protein.

Applicants respectfully point out that the claims require that the compound or agent interacts with an SV2 protein. Claim 93 requires that the test compounds or agents binds the SV2 protein, and claims 139 and 156 require the addition of LEV or an analog and derivative of LEV for competition in binding to the LBS on the SV2 protein. LEV is a well known compound and is disclosed in the specification. As discussed above, analogs and derivatives of LEV are disclosed in the specification. Accordingly, the specification provides a defined structure for the analogs and derivatives of LEV.

The Office Action cites *Univ. of California v. Eli Lilly & Co.* and *Vas-Cath Inc. v. Mahurkar* in support of their position. *Univ. of California v. Eli Lilly & Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997); *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111. Applicants respectfully point out that *Univ. of California v. Eli Lilly & Co.* is not applicable to the present claims because unlike *Univ. of California v. Eli Lilly & Co.*, the claims of the present application are not directed to products but to methods of identifying compounds and agents. The claims of the present application are not directed to compounds and agents. Moreover, as discussed above, the present specification adequately describes the SV2 proteins and LEV analogs and derivatives for use in the presently claimed methods. Also, SV2 proteins, LEV, and its analogs and derivatives are well known molecules. Accordingly, the specification complies with the written description requirement as set forth in *Vas-Cath v. Mahurkar*, and under § 112, first paragraph.

Rejection of the Claims Under 35 U.S.C. § 112, Second Paragraph

A. Claims 93-102 and 139-156 have been rejected as being incomplete for omitting essential steps.

Applicants respectfully point out that the claims as they stand include all the essential steps for identifying compound or agent that interacts with an SV2 protein. The claims recite the

essential reagents and steps for identifying the compound or agent. The compound or agent may modulate any activity of an SV2 protein.

B. Claims 93, 130-132, 135, 137, and 139 have been rejected as being indefinite for failing to define the word "modulate."

Applicants respectfully point out that the word "modulate" is understood to include enhancement or inhibition of a function. Applicant intends the term "modulate" to encompass both enhancement and inhibition of a function.

Applicants respectfully submit that breadth of a term recited in a claim does not render a claim indefinite (see MPEP 2173.04).

C. Claims 94-96 have been rejected because the metes and bounds of what is encompassed by the terms "analogs" and "derivatives" are not defined.

Applicants respectfully point out that the terms "analogs" and "derivatives" are routinely used and well known to a person having ordinary skill in the art.

Applicants would like clarification of this rejection because it appears that the Patent Office may have intended the rejection to be based on the enablement of the breadth of the terms. However, as mentioned above, the breadth of a term recited in a claim does not render a claim indefinite (see MPEP 2173.04). Moreover, the specification discusses in detail and provides examples of analogs and derivatives of LEV.

D. Claim 135 has been rejected because the metes and bounds of what is encompassed by the term "substrate" are not defined.

Applicants respectfully point out that the term "substrate" is a well-known term and is routinely used with the term "transport." As shown in the attached reference by Janz *et al.* (Neuroscience, 1999, 94(4): 1279-1290), a transporter molecule transports a substrate across the membrane. Accordingly, the claim is not indefinite for recitation of the word "substrate." Thus, the recitation of the term "substrate" does not render the claim indefinite.

E. Claims 94-102, 126-137, and 140-155 are rejected for recitation of the article "A."

Claims 94-102, 126-137, and 140-155 have been amended to replace the article "A" with "The" as suggested by the Office Action.

F. Claims 152 and 153 are rejected for failing to provide antecedent basis for "the agent."

Applicants respectfully point out that claims 152 and 153 are dependent upon claim 139 which provides antecedent basis for the term "agent."

Provisional Rejection of the Claims on the Ground of Nonstatutory Obviousness-Type Double Patenting

Claims 93-102, 139-154, and 156 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 9-12, 17-19, 22-25, 29, 35, 37-40, 45-52, 54-57, 61-68, 71-74 and 78 of copending U.S. Application 10/308,163.

Applicants respectfully point out that claims 1-4, 9-12, 17-19, 22-25, 62-68, 71-74, and 78 have been canceled in copending U.S. Application 10/308,163 and that the Application has issued as U.S. Patent 7,090,985.

Applicants respectfully submit that claims 29, 35, 37-40, 45-52, 54-57, and 61 are patentably distinct from the presently claimed invention because the present claims are directed to methods of identifying compounds and agents that interact with an SV2 protein using cell-free or membrane-free SV2 protein or fragment thereof, while the claims in the copending application are directed to methods of identifying a binding partner for an SV2A protein using recombinant host cells expressing an SV2A protein or fragment thereof. Thus, Applicants respectfully request withdrawal of the rejection.

Rejection of the Claims Under 35 U.S.C. § 102(a)

Claims 93, 97, 99, and 102 have been rejected under 35 U.S.C. § 102(a) as being anticipated by WO2003016475A2.

Applicants respectfully point out that the publication date of WO2003016475A2 is February 26, 2003 and that the earliest priority date of the present application is December 3, 2002. Thus, WO2003016475A2 does not anticipate the claims under 35 U.S.C. § 102(a).

Moreover, Applicants respectfully submit that the claims as they stand are directed to methods of identifying compounds and agents that interact with a SV2 protein using cell-free or membrane-free SV2 protein. A required step in the claimed method comprises obtaining cell-free or membrane-free SV2 protein prior to incubating the SV2 protein with a test compound or agent. In contrast, the cited reference does not teach screening assays using cell-free or membrane-free SV2 protein. The cited reference only discloses screening assays comprising contacting cells expressing SV2A protein with a test compound. Accordingly, Applicants respectfully request withdrawal of the rejection.

Rejection of the Claims Under 35 U.S.C. § 103(a)

A. Claims 93-102 and 139-156 are rejected 35 U.S.C. § 103(a) as being unpatentable over WO2003016475A2 ('475) in view of Margineanu *et al.* and Berkower.

The claims as they stand are directed to methods of identifying compounds and agents that interact with a SV2 protein using cell-free or membrane-free SV2 protein. A required step in the claimed methods comprises obtaining cell-free or membrane-free SV2 protein prior to incubating the SV2 protein with a test compound or agent.

As discussed above, '475 does not teach the use of cell-free or membrane-free SV2 protein in the screening assays. Neither Margineanu *et al.* nor Berkower cure the deficiencies of '475, since these cited references do not disclose or suggest obtaining cell-free or membrane-free SV2A protein or fragment thereof and using cell-free or membrane-free SV2A protein or fragment thereof in their binding assays.

Margineanu *et al.* disclose LEV binding assays using rat brain membranes. The assays of Margineanu *et al.* comprise contacting the rat brain membranes containing the SV2A protein with LEV. Since the SV2A protein of Margineanu *et al.* is in the rat brain membrane preparation, Margineanu *et al.* do not teach assays using cell-free or membrane-free SV2 protein or fragment thereof.

Berkower teaches the use of monoclonal antibodies for diagnosing and treating of disease. However, Berkower neither teaches SV2 proteins nor discloses screening assays using cell-free or membrane-free SV2 for identifying compounds or agents that interact with SV2 protein.

Accordingly, the combination of the cited references do not render the claimed invention obvious.

B. Claims 93-102 and 139-156 are rejected 35 U.S.C. § 103(a) as being unpatentable over WO2003016475A2 ('475) in view of Xu *et al.* and Son *et al.*

The claims as they stand are directed to methods of identifying compounds and agents that interact with an SV2 protein using cell-free or membrane-free SV2 protein. A required step in the claimed methods comprises obtaining cell-free or membrane-free SV2 protein prior to incubating the SV2 protein with a test compound or agent.

As discussed above, '475 does not teach the use of cell-free or membrane-free SV2 protein in the screening assays. Neither Xu *et al.* nor Son *et al.* cure the deficiencies of '475, since these cited references do not disclose or suggest obtaining cell-free or membrane-free SV2A protein or fragment thereof and using the cell-free or membrane-free SV2A protein or fragment thereof in their binding assays.

Xu *et al.* characterize the role of SV2A in exocytosis. However, Xu *et al.* do not teach or suggest obtaining cell-free or membrane-free SV2A protein or fragment thereof and using the cell-free or membrane-free SV2A protein or fragment thereof in screening assays for identifying compounds or agents that interact with SV2 protein.

Son *et al.* teach that SV2A forms a complex with laminin-1. However, Son *et al.* do not teach or suggest obtaining cell-free or membrane-free SV2A protein or fragment thereof and using the cell-free or membrane-free SV2A protein or fragment thereof in screening assays for identifying compounds or agents that interact with SV2 protein.

Moreover, claims 139 and 156 require the addition of LEV or an analog or derivative thereof in the screening assay for competition with binding to the LBS on the SV2 protein. The cited references do not disclose LEV or analog or derivative thereof. The cited references do not even teach that LEV interacts with SV2 proteins.

Accordingly, the cited references do not render the claimed invention obvious.

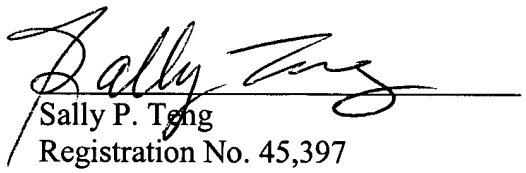
Conclusion

The foregoing amendments and remarks are being made to place the application in condition for allowance. Applicants respectfully request entry of the amendments,

reconsideration, and the timely allowance of the pending claims. A favorable action is awaited. Should the Examiner find that an interview would be helpful to further prosecution of this application, they are invited to telephone the undersigned at their convenience.

If there are any additional fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0310. If a fee is required for an extension of time under 37 C.F.R. §1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,
Morgan, Lewis & Bockius LLP



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